REMARKS

Claims 16, 22-24, and 29-34 are pending in the application, all of which stand rejected.

In the present Office Action, claims 16, 22-24, and 29-34 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite; claims 16, 22-24, and 29-34 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter; claims 16, 22-24, and 29-34 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated; and claims 16, 23-24, and 29-30 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious. Each of the Examiner's bases for rejection is addressed below, *seriatim*.

Request for Continued Examination under 37 C.F.R. 1.114

The Examiner is thanked for acknowledging the eligibility of the present application for continued examination under 37 C.F.R. 1.114, that the fee set forth in 37 C.F.R. 1.17(e) was timely paid, that the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. 1.114, and that Applicants' submission filed on August 21, 2006 has been entered.

Title of the Application

By the present Amendment and Response, the title of this application has been changed to Antibodies having Binding Specificity for the Extracellular Domain of a Breast Cancer Resistance Protein (BCRP), which is clearly indicative of the invention to which the claims are directed.

Patentability under 35 U.S.C. § 112, Second Paragraph

Claims 16, 22-24, and 29-34 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Specifically, the Examiner rejects all of the pending claims as allegedly indefinite for failing to provide a SEQ ID number for BCRP. The Examiner also points to the use of "BCRP" in the specification to refer to a protein obtained from any mammal, but to "mBCRP" or "huBCRP" when obtained from mice or humans, respectively.

Applicants respectfully traverse the stated grounds for rejection of instant claims 16, 22-24, and 29-34 and submit that the claims particularly point out and distinctly claim the subject matter of the invention. The term "BCRP" refers to a genus of proteins from individual mammalian species, as the Examiner concedes is taught by the specification. SEQ ID numbers are provided for individual species-specific BCRP sequences in the specification as filed, for example at page 8, lines 16-21, and at page 15, lines 10-16. Also, "BCRP" is defined on page 15, lines 6-7 as including "all of such ATP transport proteins obtained from any mammalian source." In the pending claims, "BCRP" is used to denote the genus of Breast Cancer Resistance Proteins, while "human or murine BCRP" is used to denote huBCRP or mBCRP.

Furthermore, Applicants submit that the amendments to claims 16, 31, and 33 obviate the Examiner's rejection. As amended, the instant claims specifically include references to "human BCRP" or huBCRP" and "murine BCRP" or "mBCRP," where appropriate, to refer to species-specific BCRPs and their respective sequences.

For these reasons, Applicants respectfully submit that the instant claims do, in fact, particularly point out and distinctly claim the subject matter of the invention and that the present bases for rejection may be withdrawn and claims 16, 22-24, and 29-34 be allowed. Applicants request that the Examiner issue a Notice to that effect.

Patentability under 35 U.S.C. § 112, First Paragraph

Claims 16, 22-24, and 29-34 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter. The Examiner concedes that the specification and claims as originally filed support "antibody that recognized an extracellular portion of BCRP, wherein said extracellular portion of the BCRP is in its natural conformation." The Examiner alleges, however, that the claim language:

> wherein the antibody binds to living MCF-7 or 3T3 cells expressing BCRP on their surface; wherein the antibody does not bind to living MCF-7 cells that do not express BCRP on their surface; and wherein the antibody does not bind to denatured BCRP (Claim 16)

"represent(s) a departure from the specification and the claims as originally filed and applicant has not pointed out where the support come(s) from."

Applicants respectfully traverse the stated grounds for rejection of instant claims 16, 22-24, and 29-34 and submit that the amended claims are fully supported by the application as originally filed. Support for the language in newly amended claim 16 may be found throughout the application as filed such as, for example, at page 39, line 5 – page 40, line 2, wherein is described the generation of hybridomas from mice immunized with 3T3-BCRP cells, screening of the hybridomas with MCF-7 cells, both transduced with an amphotrophic HaBCRP vector (screen) and untransduced cells (back-screen), and production of BCRP-specific antibodies. Further support for the recited claim language may be found at page 22, line 26 – page 24, line 17, wherein (1) methods for producing BCRP antibodies involving use of 3T3 and MCF-7 cells and (2) the use of transduced living cells to increase the probability of detection by the immune system of external huBCRP epitopes in their native conformation rather than internal epitopes or denatured epitopes are both disclosed.

Applicants, therefore, submit that instant claims 16, 22-24, and 29-34 are adequately supported by the instant specification, which reasonably conveys to the skilled artisan that Applicants were in possession of the above recited aspects of the claimed invention at the time the present application was filed. Thus, Applicants' previous amendments to claim 16 do not, in fact, constitute new matter. Accordingly, Applicants respectfully request that the present basis for rejecting claims 16, 22-24, and 29-34 under 35 U.S.C. § 112, first paragraph may be properly withdrawn and that the Examiner issue a Notice to that effect.

Patentability under 35 U.S.C. § 102(e), Novelty

Validity of Claims 16, 22, and 31-34 in view of U.S. Patent No. 6,313,277

Claims 16, 22, and 31-34 stand rejected as allegedly anticipated by U.S. Patent No. 6,313,277 (the '277 patent). The Examiner alleges that the '277 patent teaches polyclonal and monoclonal antibodies that bind to a BCRP. While the Examiner concedes that the '277 patent does not expressly disclose antibodies that (1) bind to an extracellular portion of a BCRP and (2) do not

bind to a denatured BCRP, the Examiner alleges that such functional limitations are inherent properties of the antibodies taught by the '277 patent "because the referenced antibody was obtained against the same antigen as claimed." The Examiner further alleges that the burden is on Applicants to prove otherwise given the lack of laboratory facilities at the USPTO. (Citing *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and *In re Fitzgerald et al.*, 2005 USPQ 594 (CCPA 1980)). With respect to claims 31-34, the Examiner concedes that the claims recite a process of producing a monoclonal antibody that is different from the referenced monoclonal antibody, but alleges that, since the claims are directed to a product, the patentability of the product does not depend on its method of production. (Citing *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985) and MPEP 2113)).

Applicants respectfully traverse the stated grounds for rejection of instant claims 16, 22, and 31-34, and submit that because, *inter alia*, the '277 patent does not disclose, either expressly or inherently, antibodies that (1) bind to an extracellular portion of a BCRP or (2) antibodies that do not bind to denatured BCRP, the '277 patent does not expressly or inherently disclose each element of the presently claimed invention and, consequently, cannot anticipate any of claims 16, 22, or 31-34.

Claim 16, as presently amended, is directed to:

> An isolated antibody that binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP) selected from the group consisting of human BCRP (huBCRP) or murine BCRP (mBCRP); wherein the extracellular portion of the BCRP is in its natural conformation; wherein the antibody binds to living MCF-7 or 3T3 cells expressing BCRP on their surface; wherein the antibody does not bind to living MCF-7 cells that do not express BCRP on their surface; and wherein the antibody does not bind to denatured BCRP. [Underscore added].

Claim 22 depends from and contains each of the limitations of independent claim 16. Thus, the novelty of claim 22 necessarily follows from the novelty of claim 16.

Claims 31 and 33, as presently amended, recite "[a]n isolated antibody that binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP) selected from the group

consisting of human BCRP (huBCRP) and murine BCRP (mBCRP) ... ." [Underscore added]. Claim 32 depends from and contains each of the limitations of independent claim 31 and claim 34 depends from and contains each of the limitations of independent claim 33. Thus, the novelty of claims 32 and 34 necessarily follow from the novelty of independent claims 31 and 33, respectively.

It is well established that a claimed invention, as described in appropriately constructed claims, must be the same as that of a prior art reference in order for that reference to anticipate the claims. *Glaverbel Societe Anonyme v. Northlake Marketing & Supply Inc.*, 45 F.3d 1550 (Fed. Cir. 1995). Anticipation is negated (*i.e.* the "all elements" standard is not satisfied) if any claimed element is missing in a single prior art reference, regardless of how insubstantial this element may be. (MPEP 2131). "A prior art reference anticipates a claim only if the reference discloses, either expressly or inherently, every limitation of the claim." *Rowe v. Dror*, 112 F.3d 473 (Fed. Cir. 1997) [emphasis added]. Thus, a prior art reference does not anticipate when the claim limitation or limitations not expressly found in that reference are also not inherent in it. *Atlas Powder Co. v. Ireco Inc.* 190 F.3d 1342 (Fed. Cir. 1999).

To anticipate under a theory of inherency, the prior art must "necessarily function[] in accordance with, or include[], the claimed limitations... ." *Atlas Powder* 190 F.3d 1342 [emphasis added]. Results must be the necessary consequence of what is deliberately intended. *Mehl/Biophile International Corp. v. Milgraum*, 192 F.3d 1362 (Fed. Cir. 1999) [emphasis added]. A limitation or the entire invention is inherent and in the public domain only if it is the 'natural result flowing from' the explicit disclosure of the prior art. *Perricone v. Medicis Pharmaceutical Corp.*, 432 F.3d 1368 (Fed. Cir. 2005) [emphasis added], citing *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373 (Fed. Cir. 2003), quoting *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001).

Occasional results are not, however, inherent. *Mehl/Biophile* 192 F.3d 1362. "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." MPEP § 2112 (quoting *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993) [emphasis added] (reversed rejection because inherency was based on what

would result due to optimization of conditions, not what was necessarily present in the prior art.) and citing *In re Oelrich*, 666 F.2d 578 (CCPA 1981)).

"An invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species).

Furthermore, there can be no anticipation where the record does not show conclusively that the prior art produced the claimed subject matter. *Schering Corp. v. Geneva Pharmaceuticals*, 339 F.3d 1373 (Fed. Cir. 2003) [emphasis added] (citing *Tilghman v. Proctor*, 102 U.S. 707 (1880) ("We do not regard the accidental formation of fat acid in Perkins's steam cylinder ... (if the scum which rose on the water issuing from the ejection pipe was fat acid) as of any consequence in this inquiry.") and *Eibel Process Co. v. Minn. & Ontario Paper Co.*, 261 U.S. 45, 43 S.Ct. 322 (1923) ("We find no evidence that any pitch of the wire ... had brought about such a result ... and ... if it had done so under unusual conditions, accidental results, not intended and not appreciated, do not constitute anticipation." [Underscore added].)).

The Examiner bears the burden of "provid[ing] rationale or evidence tending to show inherency." MPEP § 2112 ¶ IV. "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *Id.* quoting *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) [emphasis added; citations omitted]. "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the

applied prior art." MPEP § 2112 ¶ IV *quoting Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis added and in the original; the Board reversing the Examiner on the basis that the Examiner did not provide objective evidence or cogent technical reasoning to support the conclusion of inherency.).

In the present Office Action, the Examiner alleges, in reference to the '277 patent (col. 4, lines 50-60) that "because the referenced antibody was obtained against the same antigen as claimed," the '277 patent must inherently anticipate the instant claims. Applicants respectfully disagree and submit that the Examiner's statement, which is unsupported by any basis in fact and/or technical reasoning, fails to support a determination that antibodies capable of binding to BCRP made in the manner disclosed in the '277 patent necessarily "bind[] to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)" and/or "not bind to denatured BCRP" as recited in instant claim 16. Thus, Applicants submit that the Examiner has failed to satisfy the burden of providing "objective evidence or cogent technical reasoning" to support a conclusion of inherency.

The '277 patent discloses that "[a] polyclonal antibody capable of binding to BCRP can be prepared by immunizing a mammal with a preparation of BCRP or functional derivative of BCRP." [Col. 4, lines 50-52; underscore added]. The '277 patent also discloses that "[monoclonal] antibodies can be produced by immunizing splenocytes with activated BCRP." [Col. 4, lines 54-57]; underscore added; citation deleted]. Thus, the '277 patent does not, in fact, disclose the actual generation of any antibody.

Applicants submit that such prophetic disclosure does not support the Examiner's assertion that antibodies would necessarily "bind[] to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)" and/or "not bind to denatured BCRP" as recited in instant claim 16. There is nothing within the '277 patent from which one skilled in the art could deduce to what, if any, portion of BCRP an antibody generated by "immunizing a mammal with a preparation of BCRP or functional derivative of BCRP" or by "immunizing splenocytes with activated BCRP" would bind. Thus, the '277 patent does not "make clear that the missing descriptive matter is necessarily present in the thing described in the reference."

Applicants do not claim any antibody that binds to BCRP. Applicants specifically claim antibodies that, *inter alia*, bind to an extracellular portion of a BCRP and do not bind to a denatured BCRP. The mere possibility that an antibody generated by the methods suggested in the '277 patent might bind to "an extracellular portion of a BCRP" and/or might not bind "to denatured BCRP" is not sufficient to establish that antibodies generated by the methods disclosed in the '277 patent would necessarily possess those activities. Thus, the '277 patent cannot be said to inherently disclose the antibodies of instant claim 16.

Indeed, as pointed out by Dr. Sarkadi in his Declaration (filed Oct. 28, 2003), the '277 patent teaches antibodies prepared against a *purified* protein, not against a BCRP in its natural conformation. This is critical because BCRP adopts a "very different" conformation upon purification as compared to its natural conformation within the context of a cell membrane. Also, as Dr. Sarkadi emphasized, "with respect to the extracellular domain of BCRP, it is important to note that BCRP forms a homodimer. The BCRP homodimer would be expected to adopt a very different conformation than the monomeric purified protein or purified protein fragment. As a result, any antibody generated against a purified BCRP protein, or fragment of a BCRP protein would not be expected to recognize the extracellular domain of the BCRP protein in its natural conformation embedded in the cell membrane." [Sarkadi Declaration ¶5]. It is clear that antibodies raised against a purified protein, as disclosed in the '277 patent, would not necessarily bind to and, in fact, would most probably not bind to, the extracellular portion of a BCRP. Thus, the '277 patent cannot be said to inherently disclose antibodies according to presently claimed invention.

Furthermore, as Dr. Sarkadi explained in the Supplemental Declaration (filed Feb. 22, 2005), "[a]s antibodies can recognize conformational epitopes, the three-dimensional structure is critical for production and recognition of an epitope composed of a specific domain (*e.g.*, extracellular portion) in a particular conformation (*e.g.,* the natural conformation)." [Sarkadi Supplemental Declaration ¶5]. In support of his Supplemental Declaration, Dr. Sarkadi discussed his 2004 publication (Ozvegy-Laczka *et al.*, submitted with the Supplemental Declaration) wherein it was demonstrated that the binding of antibody 5D3 to an extracellular epitope of BCRP in its natural conformation "is dependent upon the actual conformation within the transport cycle of this

multidrug resistance protein. In contrast, an antibody generated against an N-terminal intracellular epitope of BCRP (*i.e.* BXP-21) cannot recognize BCRP in a living cell." [Sarkadi Supplemental Declaration ¶7]. Thus, Dr. Sarkadi concludes that "this method is essential to producing an antibody which recognizes an extracellular portion of BCRP in its natural conformation." *Id.*

Because the '277 patent does not disclose, either expressly or inherently, antibodies or methods for preparing antibodies that necessarily "bind[] to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)" and/or "do[] not bind to denatured BCRP," the '277 patent does not anticipate any of the instant claims. In view of the present amendments and remarks, Applicants believe that each of the Examiner's stated bases for rejection of claims 16, 22, and 31-34 under 35 U.S.C. § 102(e) as allegedly anticipated by the '277 patent have been overcome and respectfully request that the Examiner issue a Notice to that effect.

Validity of Claims 16, 22-24, and 29-34 in view of U.S. Patent No. 6,485,933

Claims 16, 22-24, and 29-34 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent 6,485,933 (the '933 patent). The Examiner alleges that the '933 patent teaches a polyclonal and monoclonal antibody that binds to BCRP. The Examiner further alleges that the '933 patent teaches that the antibody is chimeric or humanized or attached to a detectable label. While the Examiner concedes that the '933 patent does not expressly disclose antibodies that (1) bind to an extracellular portion of a BCRP and (2) do not bind to a denatured BCRP, the Examiner alleges that such functional limitations are inherent properties of the antibodies taught by the '277 patent "because the referenced antibody was obtained against the same antigen as claimed." The Examiner further alleges that the burden is on Applicants to prove otherwise given the lack of laboratory facilities at the USPTO. (Citing *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and *In re Fitzgerald et al.*, 2005 USPQ 594 (CCPA 1980)). With respect to claims 31-34, the Examiner concedes that the claims recite a process of producing a monoclonal antibody that is different from the referenced monoclonal antibody, but alleges that, since the claims are directed to a product, the patentability of the product does not depend on its method of production. (Citing *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985) and MPEP 2113)).

Applicants respectfully traverse the stated grounds for rejection of instant claims 16, 22-24, and 29-34, and submit that because, *inter alia*, the '933 patent does not disclose, either expressly or inherently, antibodies that (1) bind to an extracellular portion of a BCRP and (2) do not bind to a denatured BCRP, the '933 patent does not expressly or inherently disclose each element of the presently claimed invention and, consequently, cannot anticipate any of claims 16, 22-24, and 29-34.

Claim 16, as presently amended, is directed to:

> An isolated antibody that binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP) selected from the group consisting of human BCRP (huBCRP) or murine BCRP (mBCRP); wherein the extracellular portion of the BCRP is in its natural conformation; wherein the antibody binds to living MCF-7 or 3T3 cells expressing BCRP on their surface; wherein the antibody does not bind to living MCF-7 cells that do not express BCRP on their surface; and wherein the antibody does not bind to denatured BCRP. [Underscore added].

Claims 22-24 and 29 each depend from and contain each of the limitations of independent claim 16. Thus, the novelty of claims 22-24 and 29 necessarily follows from the novelty of claim 16. Independent claim 30 expressly recites claim 16. Thus, the novelty of claim 30 necessarily follows from the novelty of claim 16.

Claims 31 and 33, as presently amended, recite "[a]n isolated antibody that binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP) selected from the group consisting of human BCRP (huBCRP) and murine BCRP (mBCRP) ... ." [Underscore added]. Claim 32 depends from and contains each of the limitations of independent claim 31 and claim 34 depends from and contains each of the limitations of independent claim 33. Thus, the novelty of claims 32 and 34 necessarily follow from the novelty of independent claims 31 and 33, respectively.

It is well established that a claimed invention, as described in appropriately constructed claims, must be the same as that of a prior art reference in order for that reference to anticipate the claims. *Glaverbel Societe Anonyme v. Northlake Marketing & Supply Inc.*, 45 F.3d 1550 (Fed. Cir. 1995). Anticipation is negated (*i.e.* the "all elements" standard is not satisfied) if any claimed

element is missing in a single prior art reference, regardless of how insubstantial this element may be. (MPEP 2131). "A prior art reference anticipates a claim only if the reference discloses, either expressly or inherently, every limitation of the claim." *Rowe v. Dror*, 112 F.3d 473 (Fed. Cir. 1997) [emphasis added]. Thus, a prior art reference does not anticipate when the claim limitation or limitations not expressly found in that reference are also not inherent in it. *Atlas Powder Co. v. Ireco Inc.* 190 F.3d 1342 (Fed. Cir. 1999).

To anticipate under a theory of inherency, the prior art must "necessarily function[] in accordance with, or include[], the claimed limitations… ." *Atlas Powder* 190 F.3d 1342 [emphasis added]. Results must be the necessary consequence of what is deliberately intended. *Mehl/Biophile International Corp. v. Milgraum*, 192 F.3d 1362 (Fed. Cir. 1999) [emphasis added]. A limitation or the entire invention is inherent and in the public domain only if it is the 'natural result flowing from' the explicit disclosure of the prior art. *Perricone v. Medicis Pharmaceutical Corp.*, 432 F.3d 1368 (Fed. Cir. 2005) [emphasis added], citing *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373 (Fed. Cir. 2003), quoting *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001).

Occasional results are not, however, inherent. *Mehl/Biophile* 192 F.3d 1362. "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." MPEP § 2112 (quoting *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993) [emphasis added] (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art.) and citing *In re Oelrich*, 666 F.2d 578 (CCPA 1981)).

"An invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed

species has been made or whether the prior art reference merely invites further experimentation to find the species).

Furthermore, there can be no anticipation where the record does not show conclusively that the prior art produced the claimed subject matter. *Schering Corp. v. Geneva Pharmaceuticals*, 339 F.3d 1373 (Fed. Cir. 2003) [emphasis added] (citing *Tilghman v. Proctor*, 102 U.S. 707 (1880) ("We do not regard the accidental formation of fat acid in Perkins's steam cylinder ... (if the scum which rose on the water issuing from the ejection pipe was fat acid) as of any consequence in this inquiry.") and *Eibel Process Co. v. Minn. & Ontario Paper Co.*, 261 U.S. 45, 43 S.Ct. 322 (1923) ("We find no evidence that any pitch of the wire ... had brought about such a result ... and ... if it had done so under unusual conditions, accidental results, not intended and not appreciated, do not constitute anticipation." [Underscore added].)).

The Examiner bears the burden of "provid[ing] rationale or evidence tending to show inherency." MPEP § 2112 ¶ IV. "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *Id.* quoting *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) [emphasis added; citations omitted]. "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP § 2112 ¶ IV *quoting Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis added and in the original; the Board reversing the Examiner on the basis that the Examiner did not provide objective evidence or cogent technical reasoning to support the conclusion of inherency.).

In the present Office Action, the Examiner alleges, in reference to the '933 patent (col. 16, lines 15-30) that "because the referenced antibody was obtained against the same antigen as claimed," the '933 patent must inherently anticipate the instant claims. Applicants respectfully

disagree and submit that the Examiner's statement, which is unsupported by any basis in fact and/or technical reasoning, fails to support a determination that antibodies capable of binding to BCRP made in the manner disclosed in the '933 patent necessarily "bind[] to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)" and/or "not bind to denatured BCRP" as recited in instant claim 16. Thus, Applicants submit that the Examiner has failed to satisfy the burden of providing "objective evidence or cogent technical reasoning" to support a conclusion of inherency.

The '933 patent discloses that "[a] variety of protocols for detecting and measuring the expression of BCRP, using either polyclonal or monoclonal antibodies specific for the protein are known in the art." [Col. 16, lines 16-18; underscore added]. Thus, the '933 patent does not, in fact, disclose any antibody. Rather, the '933 patent discloses assay systems such as "enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS)" that could be employed to detect the expression of BCRP "using either a polyclonal or monoclonal antibod[y]."

Applicants submit that such prophetic disclosure of purely hypothetical antibodies does not support the Examiner's assertion that antibodies would necessarily "bind[] to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)" and/or "not bind to denatured BCRP" as recited in instant claim 16. There is nothing within the '933 patent from which one skilled in the art could deduce to what, if any, portion of BCRP an antibody generated by "immunizing a mammal with a preparation of BCRP or functional derivative of BCRP" or by "immunizing splenocytes with activated BCRP" would bind. Thus, the '933 patent does not "make clear that the missing descriptive matter is necessarily present in the thing described in the reference."

Applicants do not claim any antibody that binds to BCRP. Applicants specifically claim antibodies that, *inter alia*, bind to an extracellular portion of a BCRP and do not bind to a denatured BCRP. The mere possibility that a hypothetical antibody suggested in the '933 patent might bind to "an extracellular portion of a BCRP" and/or might not bind "to denatured BCRP" is not sufficient to establish that such hypothetical antibodies would necessarily possess those activities. Thus, the '933 patent cannot be said to inherently disclose the antibodies of instant claim 16.

Because the '933 patent does not disclose, either expressly or inherently, any antibodies or methods for preparing any antibodies that necessarily "bind[] to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)" and/or "do[] not bind to denatured BCRP," the '933 patent does not anticipate any of the instant claims. In view of the present amendments and remarks, Applicants believe that each of the Examiner's stated bases for rejection of claims 16, 22-24, and 31-34 under 35 U.S.C. § 102(e) as allegedly anticipated by the '933 patent have been overcome and respectfully request that the Examiner issue a Notice to that effect.

Patentability under 35 U.S.C. § 103(a), Nonobviousness

Validity of Claims 16, 23-24, and 29 over the '277 Patent in view of Owens et al.

Claims 16, 23, 24, and 29 stand rejected as allegedly obvious over the '277 patent in view of Owens *et al.*, *J. of Immunological Methods* 168:149-165 (1994) [Owens]. The Examiner concedes that the '277 patent does not teach an isolated antibody wherein the antibody is chimeric (as recited in claim 23) or humanized (as recited in claim 24) or attached to a detectable label (as recited in claim 29). The Examiner alleges, however, that Owens remedies these deficiencies by teaching modification of murine antibodies such as chimeric antibodies, single chain antibodies, humanized antibodies, or attaching a detectable label to an antibody. Thus, the Examiner alleges that it would have been obvious to a person having skill in the art to combine the teachings of the '277 patent and of Owens to achieve Applicants' invention and that the person of skill in the art would have been motivated to make such a combination because of the various advantages of each antibody type over unmodified antibodies, and that they would have had a reasonable expectation of success in doing so.

Applicants respectfully traverse the stated grounds for rejection and submit that the combination of the '277 patent and Owens, viewed as a whole, neither teaches nor suggests the subject matter recited by presently amended claims 16, 23-24, and 29.

As addressed in the previous section, "Patentability under 35 U.S.C. § 102(e), Novelty," and as conceded by the Examiner, the '277 patent "is silent" with respect to antibodies that (1) bind to an extracellular portion of a BCRP and (2) do not bind to a denatured BCRP. Because Owens does

not, *inter alia*, remedy these deficiencies in the '277 patent, none of claims 16, 23-24, and 29 can be obvious over the '277 patent in view of Owens. On the contrary, Owens' teachings with respect to antibodies are generalized with respect to any antibody and fail to provide any guidance to the skilled artisan otherwise motivated to generate an antibody to BCRP. Even assuming, *arguendo*, that the Examiner is correct in alleging that "it would have been prima facie obvious…to produce the monoclonal antibody taught by US Patent '277 as chimeric, humanized antibody, taught by the Owens *et al*," such a teaching would not have lead the skilled artisan to Applicants' claimed invention because neither reference teaches or suggests an antibody that (1) binds to an extracellular portion of a BCRP and (2) does not bind to a denatured BCRP.

The Examiner's allegations fail to appreciate the distinction between antibodies suggested in the '277 patent that are proposed to be generated against a purified BCRP versus antibodies that bind to an extracellular portion of a BCRP but not to a denatured BCRP. As discussed above in reference to Dr. Sarkadi's Declaration, "any antibody generated against a purified BCRP protein, or fragment of a BCRP protein would not be expected to recognize the extracellular domain of the BCRP protein in its natural conformation embedded in the cell membrane." [Sarkadi Declaration ¶5].

Because the '277 patent fails to teach or suggest antibodies that (1) bind to an extracellular portion of a BCRP and (2) do not bind to a denatured BCRP and because Owens fails to remedy this deficiency, Applicants respectfully submit that each of claims 16, 23-24, and 29 are nonobvious over the '277 patent in view of Owens when these references are viewed for the whole of their teachings. Applicants request that the present bases for rejecting claim 16, 23-24, and 29 be withdrawn and that the Examiner issue a Notice to that effect.

Validity of Claims 16 and 30 over the '277 Patent or the '933 Patent in view of U.S. Patent No. 4,281,061

Claims 16 and 30 stand rejected as allegedly obvious over either the '277 patent or the '933 patent in view of U.S. Patent No. 4,281,061 (the '061 patent). The Examiner concedes that neither the '277 patent nor the '933 patent teaches a kit. The Examiner alleges, however, that the '061

patent remedies that deficiency by teaching that reagents of pharmaceutical compositions can be provided as kits. Thus, the Examiner alleges that it would have been obvious to combine the teachings of either of the '277 or '933 patents with the kit of the '061 patent to achieve Applicants' claimed invention.

Applicants respectfully traverse the stated grounds for rejection and submit that the combination of either the '277 patent or the '933 patent in view of the '061 patent neither teaches nor suggests the subject matter recited by either of claims 16 or 30.

As addressed in the previous section, "Patentability under 35 U.S.C. § 102(e), Novelty," and as conceded by the Examiner, the '277 patent and the '933 patent "are silent" with respect to antibodies that (1) bind to an extracellular portion of a BCRP and (2) do not bind to a denatured BCRP. Because the '061 patent does not, *inter alia*, remedy these deficiencies in the '277 and '933 patents, neither of claims 16 or 30 can be obvious over the '277 patent or '933 patents in view of the '061 patent. On the contrary, the '061 patent's teachings with respect to "pharmaceutical compositions provided as kits" are generalized with respect to double antibodies for enhanced sensitivity in immunoassays and fail to provide any guidance to the skilled artisan otherwise motivated to generate a kit comprising an antibody to BCRP. Even assuming, *arguendo*, that the Examiner is correct in alleging that "[o]ne of ordinary skill in the art at the time of the invention was made…[would have been motivated to assemble] the reagents in a kit format" as allegedly taught by the '061 patent, such a teaching would not have lead the skilled artisan to Applicants' claimed invention because the '061 reference neither teaches nor suggests an antibody that (1) binds to an extracellular portion of a BCRP and (2) does not bind to a denatured BCRP.

The Examiner's allegations fail to appreciate the distinction between antibodies suggested in the '277 and '933 patents that are proposed to be generated against a purified BCRP versus antibodies that bind to an extracellular portion of a BCRP but not to a denatured BCRP. As discussed above in reference to Dr. Sarkadi's Declaration, "any antibody generated against a purified BCRP protein, or fragment of a BCRP protein would not be expected to recognize the

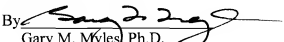
extracellular domain of the BCRP protein in its natural conformation embedded in the cell membrane." [Sarkadi Declaration ¶5].

Because the '277 patent and the '933 patent both fail to teach or suggest antibodies that (1) bind to an extracellular portion of a BCRP and (2) do not bind to a denatured BCRP and because the '061 patent fails to remedy this deficiency, Applicants respectfully submit that each of claims 16 and 30 are nonobvious over the '277 patent or the '933 patent in view of the '061 patent when these references are viewed for the whole of their teachings. Applicants request that the present bases for rejecting claim 16 and 30 be withdrawn and that the Examiner issue a Notice to that effect.

In view of the above amendments and remarks, Applicants believe the pending application is in condition for allowance; request that the pending claims as amended be allowed, and that the case be passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: March 30, 2007

Respectfully submitted,

By 
Gary M. Myles, Ph.D.
Registration No.: 46,209

DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(206) 262-8927
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant